REMARKS

Claim 1 is pending in the instant application. Claim 1 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Ueno et al. (1988), in view of U.S. Patent 4,624,965 ('965). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to employ a dose of chlorpheniramine in a method of treating motion sickness as taught by Ueno et al., while one of skill would have been motivated to alter the dose employed based on the teachings of the '965 patent where it is taught that a similar compound, brompheniramine, is used in a lower dose to treat motion sickness. The Examiner suggests that lowering the dose of chlorpheniramine to a lower dose to treat motion sickness would be obvious since lowering the dose would also lower the side effects associated with the agent. Applicants respectfully disagree with the Examiner's conclusions regarding this combination of references.

As discussed in the previous reply dated 11/21/2006, Ueno et al. (1988) disclose use of several different drugs, including chlorpheniramine, to treat symptoms of motion sickness in an animal model for motion sickness. The chlorpheniramine was administered subcutaneously at a dose of 20 mg/kg. Nowhere does this reference teach use of any other dose of chlorpheniramine,

especially not a dose that is 2 orders of magnitude lower than 20 mg/kg. It should be noted that a 12 mg dose in a human, as is claimed in amended claim 1, is equivalent to a dose of about 0.2 mg/kg (12 mg divided by average human body weight of 70 kg). Also as discussed in the previous reply dated 11/21/2006, U.S. Patent No. 4,624,965 discloses administration of therapeutic agents nasally as anti-emetic and anti-nausea agents. Brompheniramine is mentioned as one of a group of selected agents. The patent teaches administration of from 5 to 75 mg of the agents nasally. However, the only data provided showing the actual anti-nausea effects of drugs are for metoclopramide or diphenhydramine. Nowhere does the '965 patent teach or suggest administration of any agent by a route other than intranasally, nor actual efficacy or pharmacological effect data on the use of the specific agent suggested by the Examiner, brompheniramine, at any dose. Therefore, the Examiner's positions regarding these references lack any basis in standards of basic pharmacology, the standards that would be applied by one of skill in the art.

First, it is a general principle of pharmacology, taught in basic textbooks (e.g., *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York) that a pharmacological effect of a drug, its efficacy, is defined by the principle of dose-response. In the case of a drug such as chlorpheniramine, a drug that produces its effects through activity on receptors (see chapter 25 of *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E.

Limbird (eds.), McGraw Hill: New York), a dose-response relationship is defined routinely as an s-shaped curve (see page 39 of chapter 2 from *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York). With such a dose-response relationship, pharmacological activity, or drug efficacy, increases as dose increases, in a steady, almost linear manner at some doses. However, at very low doses, there is often no detectable activity. As a result, it is not supported by general principles of pharmacology that one of skill would understand or expect that a dose of a drug that is 2-orders of magnitude lower than a tested dose would produce a pharmacological effect or have efficacy, as has been suggested by the Examiner. Without any data provided on the response of chlorpheniramine at a dose near to the claimed dose, within an order of magnitude, it is not possible for one of skill to make or use the claimed invention at the much lower claimed dose. One of skill would lack an expectation of success as well as a motivation to try such a low dose.

Second, it is a general principle of pharmacology that efficacy of a drug is effected by the route of administration. In the case of the instant invention, the Examiner has suggested that data from intranasal administration of a different drug predict what one of skill would expect to see with an entirely different drug administered by an entirely different route. In the specification as filed, the data provided to enable the claimed invention is based on administration of chlorpheniramine orally to humans. In the '965 patent cited by the Examiner, the

drugs metoclopramide or diphenhydramine were shown to have anti-nausea effects when administered intranasally at doses of between 5 and 75 mg, not orally. No data on efficacy, by any route of administration, are provided for brompheniramine as suggested by the Examiner. It is also a general principle of pharmacokinetics (the scientific discipline that studies how a drug arrives at its site of action to produce its effects, and how a route of administration affects the required effective dose of a drug) that a drug administered intranasally would have a different dose-response relationship for efficacy than that same drug would have if administered orally (see chapter 1 of *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York). For example, it is well-established that lower doses of a drug are administered intranasally in order to produce the same magnitude of efficacy/effects that are seen following oral administration (Salib, R.J. and P.H. Howarth. 2003. *Drug Safety* 26:863-893; see abstract). Therefore, contrary to the Examiner's suggestion, one of skill would not use data on intranasal administration of any drug to predict a dose level that would be effective orally for the same drug, let alone an entirely different drug (brompheniramine).

This is further supported by an example of an FDA-approved intranasal anti-histamine agent, azelastine. Azelastine is a drug that is available as an intranasal formulation for treatment of allergic rhinitis that is from a different chemical class than chlorpheniramine, but like chlorpheniramine, has histamine receptor blocking activity (Salib, R.J. and P.H.

Howarth. 2003. *Drug Safety* 26:863-893; see page 870). The recommended effective intranasal dose of azelastine is about 255 micrograms twice a day (2 sprays of 137 micrograms twice a day; Salib, R.J. and P.H. Howarth. 2003. *Drug Safety* 26:863-893; see page 870). In contrast, the effective oral dose of azelastine is described in the published medical literature to be in the range of 4 to 8 milligrams twice of day (Riethmuller-Winzen, H. et al. 1994. *Arzneimittalforschung* 44:1136-1140; see abstract). Therefore, the effective intranasal dose is 20 times lower than the dose shown to be effective orally. The Examiner is thus incorrect in suggesting that the '965 patent provides useful data for one of skill to set a dose of chlorpheniramine for use orally. The '965 patent provides data on entirely different drugs (metoclopramide and diphenhydramine) given intranasally. This patent can only inform one of skill about what is known concerning intranasal dosing, namely that drugs can be administered intranasally at lower doses than are given orally and would be expected to have efficacy at these lower doses if given intranasally.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the cited prior art fails to teach the invention as claimed which is use of

chlorpheniramine at a specific dose to decrease the signs and symptoms of motion sickness. The art, when combined, teaches use of chlorpheniramine only at much higher doses, 2 orders of magnitude higher doses, or teaches use of entirely different drugs intranasally. One of skill would not expect that data on an entirely different drug given by the intranasal route would suggest that chlorpheniramine given orally at 12 mg would be an effective drug to decrease the signs and symptoms of motion sickness. The Examiner's conclusions are without basis in the general principles and standards of pharmacology. Accordingly, the prior art references cited fail to establish a case of prima facie obviousness. Withdrawal of this rejection is respectfully requested.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Advisory Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Date: **May 7, 2007**

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